APPENDIX 3

Appendix 3: Review of Pfizer Early Alert Safety Database

Summary

The Pfizer-sponsored clinical trial database is a rigorous source of data to monitor occurrences of congestive heart failure (CHF), myocardial infarction, and stroke. Although the review of the clinical trial data did not show any signal with regard to these selected cardiovascular events, a comprehensive review of the early alert safety database was undertaken for CHF or heart failure-like events, myocardial infarction-like events and stroke-like events as supportive evidence.

A search of the Pfizer early alert safety database identified 99 serious clinical study cases reporting cardiovascular events that were thought to be related to doxazosin or doxazosin GITS by the investigator and/or Pfizer. Of these, seven cases involved heart failure-like events, 18 involved stroke-like events, and 13 involved myocardial infarction or related events. Due to multiple events in three cases, there were 34 discrete cases that reported these three types of events. In nearly all of the 34 cases, the patients had at least one concomitant medication or medical history suggestive of pre-existing cardiovascular disorders or other risk factors associated with these events. The treatment indication in all but one of the 34 cases was hypertension. Therefore, these patients appeared to be at high risk of developing heart failure, stroke, myocardial infarction, or related events independent of doxazosin or doxazosin GITS therapy. In addition, based on review of the cases in which the patient was reported to have died regardless of causality, there is no signal indicating that doxazosin or doxazosin GITS therapy places patients at increased risk of death.

A search of the non-clinical-study cases identified a total of 11,359 doxazosin / doxazosin GITS cases, of which there were 190 cases of possible stroke-like events, 154 cases of myocardial infarction-like events and 148 cases of heart failure-like events. It should be noted that during the 13 years that doxazosin has been commercially available when these cases were reported, there has been approximately 4.1 billion patient-days of doxazosin therapy.

The 148 non-clinical study cases reporting heart failure-like events were reviewed. These cases involved 1.3% of all doxazosin/doxazosin GITS cases entered into the database, with a reporting rate of 36 cases/billion patient-days of therapy. The 58 relevant cases of heart failure-like events were further reviewed. The majority of patients was male and elderly, and most had medical histories that appear to have placed the patients at high risk for heart failure-like events independent of doxazosin or doxazosin GITS therapy. In 16 cases the patients were reported to have died, seven of which originated from marketing-based patient compliance programs that involved solicitation of information from consumers. Given that most of the patients were male and elderly, and many were reported to have medical histories that would place them at high risk of heart-failure-like events, there was no signal of a causal relationship with doxazosin or doxazosin GITS.

The 154 non-clinical-study cases reporting myocardial infarction-like events were reviewed. These cases involved 1.4% of all doxazosin/doxazosin GITS cases entered into

the database, with a reporting rate of 36 cases/billion patient-days of therapy. Of these, there were 128 relevant cases that were further reviewed. This dataset was notable for the nearly 75% of cases originating from marketing-based patient compliance programs. These were reported by consumers and most lacked information regarding concomitant medication and medical history. Most of these patients were male, over 50 years of age, and had risk factors for developing myocardial infarction-like events independent of doxazosin or doxazosin GITS therapy, based on significant medical histories and relevant concomitant therapies. There were 54 patients who were reported to have died, and this outcome did not appear to be associated with doxazosin therapy in these cases. Given that most patients were at risk for myocardial infarction-like events, and the majority of these cases originated from marketing-based patient compliance programs and lacked key information regarding concomitant medication and/or medical history, there was no signal of a causal relationship with doxazosin or doxazosin GITS.

The 190 non-clinical study cases reporting stroke-like events were reviewed. These cases involved 1.7% of all doxazosin/doxazosin GITS cases entered into the database, with a reporting rate of 46 cases/billion patient-days of therapy. Of these, there were 170 relevant cases that were further reviewed. Over half of these cases originated from marketing-based patient compliance programs. Most of these patients were male and elderly. The majority of patients had a medical history or were taking concomitant medications(s) suggestive of concurrent illness that could have predisposed them to stroke or stroke-like events independent of doxazosin or doxazosin GITS therapy. There were 37 patients who were reported to have died, and this outcome did not appear to be associated with doxazosin therapy in these cases. Given that most patients were at risk for these events, there was no signal of a causal relationship with doxazosin or doxazosin GITS.

The number of cases reported to Pfizer that involved heart failure, myocardial infarction and stroke-like events was relatively small compared to all reported cases of adverse events. The characteristics of the patients, as well as their reported medical histories and concomitant medication(s) place them at high risk of experiencing these selected cardiovascular events independent of doxazosin or doxazosin GITS therapy. The number of cases reporting these selected cardiovascular events is small considering more than 4.1 billion patients-days of doxazosin therapy over 13 years of worldwide commercial use. Review of the cases reporting CHF and heart failure-like events, myocardial infarction-like events and stroke-like events supports the conclusion of the review of Pfizer's clinical trial databases that there is no signal of a causal relationship between these events and doxazosin or doxazosin GITS therapy.

Description of Early Alert Safety Database

Pfizer's early alert safety database contains cases of adverse events reported spontaneously to Pfizer, cases reported from adverse event registries, cases of adverse events published in the medical literature, and cases of serious adverse events reported from clinical studies regardless of causality.

Spontaneous reports by their nature are of lesser scientific rigor than clinical trial data. Limitations of spontaneous reporting includes duplicate and second-hand reporting; variable expertise of reporters; incomplete information reported including uncertain drug ingestion; unsubstantiated reports/anecdotes; inability to use reports to determine incidence; and inability to use reports to assess causality. However, spontaneous reports draw from very large number of patients, reflect real-world usage situations, and provide a means for detecting rare events that are not captured in usual clinical trials.

Methodology

The early alert safety database was reviewed for cases that involved cardiovascular adverse events entered into the database through 28 February 2001. For the purposes of this review, cardiovascular adverse events were defined as any event that coded to WHO-ART preferred adverse event terms listed under the "cardiovascular, general", "heart rate/rhythm", "myo-, endo-, pericardial & valve" and "vascular (extracardiac)" body systems, as well as the preferred adverse event terms "sudden death" and "pulmonary edema." For the purpose of this review, heart failure-like events were defined as events that coded to the WHO-ART preferred adverse event terms "cardiac failure", "cardiac failure left", "cardiac failure right", "cardiomegaly", "cardiomyopathy", "circulatory failure", "hypertension pulmonary", "pulmonary edema", and "worsening heart failure". Myocardial infarction or related events were defined as events that coded to the WHO-ART preferred adverse event terms "myocardial infarction", "myocardial rupture (post infarct)", and "thrombosis coronary". Stroke-like events were defined as events that coded to the WHO-ART preferred adverse event terms "cerebral hemorrhage", "cerebrovascular disorder", "embolism cerebral", "hemorrhage intracranial", "subarachnoid hemorrhage", "thrombophlebitis cerebral vein", "thrombosis carotid", "thrombosis cerebral", and "thrombosis cerebral arterial".

For clinical study cases, the database was reviewed for doxazosin, doxazosin GITS, comparison agents, or blinded therapy cases from Pfizer-sponsored doxazosin or doxazosin GITS clinical studies. These cases were further reviewed for cases in which either the investigator or Pfizer attributed causality or relatedness of the event to doxazosin or doxazosin GITS. The doxazosin/doxazosin GITS cases were also reviewed for all cases where the patient was reported to have died regardless of causality. For non-clinical-study cases, the database was reviewed for doxazosin and doxazosin GITS cases.

Pfizer-Sponsored Clinical Study Cases

Results – Pfizer-Sponsored Clinical Study Cases

There were a total of 1,353 serious cases from Pfizer-sponsored doxazosin and doxazosin GITS clinical trials entered into the database through 28 February 2001. These cases were reported from all Pfizer-sponsored clinical studies (including placebo- or active-controlled studies, and open, non-comparative studies) involving more than 100,000 patients. (For a discussion of the occurrence of adverse events during controlled clinical studies, see Section 2 – Review of Pfizer-Sponsored Clinical Trials.) Among these cases

were 1,031 doxazosin cases, 136 doxazosin GITS cases, 142 cases treated with comparative agents, and 44 cases treated with blinded therapy. Hypertension (defined as indications coding to the ICD-9 diagnosis code "hypertensive disease") was the indication for treatment in 852 of these cases. Benign prostatic hyperplasia (BPH, defined as indications coding to the ICD-9 diagnosis code "hyperplasia of prostate") was the indication for 465 of the cases. Of the 658 cases reporting at least one adverse cardiovascular event, 501 reported hypertension as the treatment indication and 161 reported BPH as the treatment indication. Information for these cases is summarized in Table 3.1 (below).

Table 3.1 Doxazosin, Doxazosin GITS and Comparator Cases of Cardiovascular Adverse Events Reported From All Pfizer-Sponsored Clinical Studies[1] Entered Into Pfizer's Early Alert Safety Database Through 28 February 2001.

Case Criteria	Number of Cases (% of All Cases)				
	Doxazosin	Doxazosin GITS	Active Comparators	Placebo	Blinded Therapy
Hypertension Cases	706	75	45	9	17
BPH Cases	305	58	30	55	17
Cases With Heart Failure-Like Events	68	8	2	0	0
Cases With Stroke-Like Events	99	10	7	4	2
Cases With Myocardial Infarction or Related Events	141	9	9	1	2
Cases with Adverse Cardiovascular Events	542[2]	54[3]	33[4]	14	15
All Cases	1,031[5]	136[6]	76[7]	66	44

1-These cases were reported from all Pfizer-sponsored clinical studies (including placebo- or active-controlled studies, and open, non-comparative studies) involving more than 100,000 patients.
2 - Includes 518 cases with doxazosin alone, 8 cases with doxazosin and blinded therapy, 1 case with doxazosin and doxazosin GITS, 1 case with doxazosin and enalapril, 1 case with doxazosin and hydrochlorothiazide, 12 cases with doxazosin and finasteride, and 1 case with doxazosin and verapamil.
3 - Includes 53 cases with doxazosin GITS alone and 1 case with doxazosin GITS and captopril.
4 - Includes 3 cases with alfluzosin, 7 cases with atenolol, 3 cases with bendrofluazide, 2 cases with enalapril, 6 cases with finasteride, 6 cases with hydrochlorothiazide, 1 case with lisinopril, 3 cases with nifedipine, 1 case with terazosin and 1 case with verapamil.
5 - Includes 968 cases with doxazosin alone, 31 cases with doxazosin and blinded therapy, 1 case of doxazosin and doxazosin GITS, 3 cases with doxazosin and enalapril, 25 cases with doxazosin and finasteride, 2 cases with doxazosin and hydrochlorothiazide and 1 case with doxazosin and verapamil.
6 - Includes 135 cases with doxazosin GITS alone and 1 case with doxazosin GITS and captopril.
7 - Includes 4 cases with alfluzosin, 1 case with amlodipine, 11 cases with atenolol, 4 cases with bendrofluazide, 2 cases with bendrofluazide and potassium, 3 cases with enalapril, 22 cases with finasteride, 14 cases with hydrochlorothiazide, 2 cases with lisinopril, 6 cases with nifedipine, 1 case with tamsulosin, 4 cases with terazosin and 2 cases with verapamil.

Among the 658 cases reporting adverse cardiovascular events, there were 99 cases (86 doxazosin and 13 doxazosin GITS) in which the investigator and/or Pfizer attributed causality or relatedness of the events to doxazosin or doxazosin GITS therapy. The characteristics of these 99 cases are summarized in the Table 3.2 (below).

Table 3.2. Serious Cases of Cardiovascular Adverse Events From Pfizer-Sponsored Clinical Studies In Which Causality or Relatedness was Attributed to Doxazosin or Doxazosin GITS Therapy		
Characteristic		**Number of Cases**
Gender	Male	54
	Female	45
Age (years) Range: 39-81	≤ 50	6
	≥ 51 to ≤ 70	66
	≥ 71	27
Indication	Hypertension	89
	Benign prostatic hyperplasia	10
Dose of doxazosin standard /doxazosin GITS at onset of event	1 mg	23
	2 mg (standard/GITS)	30 / 3
	3mg	3
	4mg (standard/GITS)	19 / 8
	5mg	1
	6mg	6
	8 mg (standard/GITS)	11 / 2
	16 mg	6
Duration of therapy Prior to event	≤ 7 days	23
	8-60 days	28
	61-365 days	36
	≥ 366 days	1
	Unknown	11
Outcome of Adverse event	Resolved/improved	63
	Persisted	1
	Worsened	1
	Disability	11
	Death	7
	Unknown	16
Adverse Cardiovascular event*	Angina Pectoris / Angina Pectoris Aggravated	16
	Cerebrovascular Disorder	15
	Syncope	14
	Hypotension / Hypotension Postural	13
	Myocardial Infarction/ Thrombosis Coronary	13
	Chest Pain	11
	Fibrillation Atrial / Ventricular	10
	Tachycardia / Tachycardia Ventricular	8
	Arrhythmia / Arrhythmia Ventricular	6
	Cardiac Failure	6
	Hypertension	4
	Edema	3
	Bundle Branch Block	2
	Extrasystoles / Extrasystoles Supraventricular	2
	Palpitation	2
	Aneurysm	1
	Bradycardia	1
	Circulatory Failure	1
	Coronary Artery Disorder	1
	Pulmonary Edema	1
	Sudden Death	1

Table 3.2. Serious Cases of Cardiovascular Adverse Events From Pfizer-Sponsored Clinical Studies In Which Causality or Relatedness was Attributed to Doxazosin or Doxazosin GITS Therapy		
Characteristic		**Number of Cases**
Relevant concomitant medication*	Cases reporting use of relevant concomitant medications: Nifedipine (11), atenolol (7), digitoxin (7), enalapril (6), metoprolol (6), aspirin (5), furosemide (5), glibenclamide (4), hydrochlorothiazide (4), nitroglycerin (4), pentoxifylline (3), simvastatin (3), verapamil (3), albuterol (2), amiloride/ hydrochlorothiazide (2), captopril (2), digoxin (2), magnesium oxide/acetylsalicylic acid (2), terbutaline (2), trichloromethiazide (2), amlodipine, carbimazole, captopril/ hydrochlorothiazide, chlorpropamide, insulin, isosorbide mononitrate, isosorbide dinitrate, labetalol, medigoxin, molsidomine, oxprenolol, potassium, prazosin, propranolol, quinapril, salicylic acid, theophylline, thyroxine	50
Relevant medical history*	Cases reporting relevant medical history: Myocardial insufficiency (10), coronary heart disease (9), diabetes (9), hyperlipidemia (7), left ventricular hypertrophy (7), angina (4), stroke (4), hypercholesterolemia (3), hyperlipoproteinemia, hypertension (3), tobacco smoking (3), angina pectoris or myocardial infarction (2), atrial fibrillation (2), cerebrovascular accident (2), chest pain (2), heart failure (2), myocardial infarction (2), alcohol dependency, aortic aneurysm, apoplexy, arterial occlusive disease, cerebral hemorrhage, chronic renal insufficiency, elevated cholesterol, hyperthyroidism, increased angina symptoms, occasional raised blood sugar, orthostatic hypotension, paroxysmal arrhythmia/ fibrillation, questionable transient ischemic attack, retrosternal pain, suspected angina pectoris,	44

*More than one in some cases

Among the 99 cases, there were seven cases that reported heart failure-like events, 13 cases that reported myocardial infarction or related events, and 18 cases that reported stroke-like events. Due to multiple events in three cases, there were 34 discrete cases reporting these events.

One case (#9000711) reported cardiac failure, myocardial infarction, and cerebral embolism. The 63-year-old male patient had a history of left ventricular hypertrophy prior to treatment with doxazosin for hypertension.

Two cases reported both cardiac failure and myocardial infarction (#9000181, 9001224). The patients in these cases were males aged 76 and 79 years who were being treated with doxazosin for hypertension. The patient in case #9000181 had a history of left ventricular hypertrophy and was reported to have died due to an acute myocardial infarction and cardiogenic shock.

The patients in the four remaining cases that reported heart failure-like events were three females and one male ranging in age from 69 to 80 years. The patients in all four cases were being treated for hypertension, which is a risk factor for the development of congestive heart failure. The 80-year-old female in case #9610185 had a history of

hypercholesterolemia and was taking salicylic acid, simvastatin, and a diuretic concomitantly. Case #9000960 reported congestive heart failure in a 69-year-old female, which, according to physicians who treated her, was probably due to long-lasting hypertension or rheumatic valve disease and exacerbated by piroxicam and atenolol. She was also taking nifedipine, enalapril, digitoxin, and verapamil concomitantly. The 72-year-old male in case #9000720 who experienced pulmonary edema had a history of heart failure and a myocardial infarction prior to doxazosin therapy. The 80-year-old female who developed heart failure in case #9000376 had a history of diabetes, cardiac insufficiency, and coronary heart disease.

The remaining ten cases reporting myocardial infarction or related events involved seven males and three females ranging in age from 60 to 76 years. One case (#9000690) reported coronary artery occlusion in a 60-year-old male who took doxazosin for only three days for hypertension. Nine cases reported myocardial infarction. In one case (#9401611), the 72-year-old male patient was treated with doxazosin for BPH and experienced a myocardial infarction approximately three months after the initiation of therapy. He was not reported to be taking any additional medication and his only reported medical history was occasional raised blood sugar. The remaining eight patients were treated for hypertension, a risk factor for myocardial infarction. Two cases reported medical histories indicative of dyspnea and chest pain, which is suggestive of pre-existing coronary heart disease (#9000310), and arterial occlusive disease and hyperlipoproteinemia (#9000461). The patient in case #9000461 died due to the myocardial infarction.

The patients in the 17 remaining cases reporting stroke-like events included eleven males and six females ranging in age from 48 to 80 years. All were being treated for hypertension, which is a major risk factor for stroke. In eight cases (#R-1M791, 8900988, 9000159, 9000186, 9000872, 9000935, 9000959, 9100049), the patients' medical history indicated one or more additional risk factors for stroke, including poor blood pressure control, diabetes, previous stroke, cardiac insufficiency, and coronary heart disease. In three (#8900707, 9000728, 9727674) of the cases which did not report additional risk factors for stroke, the patients' medical history was unknown. Three of the 17 patients were reported to have died. Two died due to cerebral hemorrhage (#LOC 8900494, 9000723) and the third died approximately two years after the reported stroke of an unknown cause (#9000935).

Results – All Cause Mortality from Pfizer Sponsored Clinical Study Cases

A search of Pfizer's early alert safety database revealed 192 cases (169 doxazosin and 23 doxazosin GITS) clinical study cases in which the patient was reported to have died, regardless of causality. These cases are summarized in Table 3.3 (below).

Table 3.3. Doxazosin/ Doxazosin GITS Pfizer-Sponsored Clinical Study Cases in which the Patient Was Reported to Have Died Entered Into Pfizer's Early Alert Safety Database Through 28 February 2001

Characteristic		Number of Cases
Gender	Male	137
	Female	48
	Unknown	7
Age (years) Range: 28-96	≤ 50	15
	≥ 51 to ≤ 70	95
	> 70	75
	Unknown	7
Indication*	Acute myocardial infarction	4
	Benign prostatic hyperplasia	45
	Benign neoplasm of adrenal gland	1
	Chronic ischemic heart disease	1
	Control in clinical research	1
	Diabetic nephropathy	1
	Hypercholesterolemia	1
	Hypertension	146
	Unknown	2
Dose of doxazosin standard /doxazosin GITS at onset of event	0.5 mg	2
	1 mg	45
	2 mg	55
	3 mg	1
	4 mg (standard/GITS)	43 / 22
	6mg	2
	8 mg (standard/GITS)	6 / 1
	12 mg	1
	16 mg	3
	Post therapy	2
	Unknown	9
Duration of therapy Prior to event	≤ 7 days	5
	8-60 days	49
	61-365 days	74
	≥ 366 days	14
	Unknown	50

Table 3.3. Doxazosin/ Doxazosin GITS Pfizer-Sponsored Clinical Study Cases in which the Patient Was Reported to Have Died Entered Into Pfizer's Early Alert Safety Database Through 28 February 2001		
Characteristic		**Number of Cases**
Cause of death*	Arteriosclerotic cardiovascular disease/ coronary artery disease/ chronic heart disease/ ischemic heart disease/ syndrome of superior cava vein	6
	Apnea	1
	Arrhythmia/ ventricular fibrillation	2
	Asthma/ status asthmaticus/ bronchitis/ bronchospasm/ emphysema/ pneumonia/ bronchopneumonia/ pulmonary failure/ respiratory failure/ pulmonary infection	19
	Cancer/ tumor	30
	Cardiac arrest / cardiac shock/ cardiogenic shock/ cardiac tamponade/ cardio-respiratory arrest	8
	Cardiac failure/ acute cardiac failure/ cardiac insufficiency/ cardiovascular failure/ congestive heart failure/ circulatory failure/ pulmonary edema/ left ventricular hypertrophy	25
	Cerebral sclerosis/ encepthalomalacia/ encephalorrhagia/ organic brain disease/ post anoxic encephalopathy	4
	Cerebrovascular disorder/ suspected cerebrovascular disorder/ cerebrovascular accident/ cerebral hemorrhage/ subarachnoid hemorrhage/ cerebral infarction/ stroke/ severe apoplexy/ acute cerebral circulation disorder	18
	Cor pulmonale	1
	Diabetes/ diabetic coma/ progression of diabetic neuropathy	3
	Deterioration of general condition/ cachexia/ geromarasmus	3
	Homicide/ suicide	4
	Hypertension	2
	Liver failure/ renal failure/ renal insufficiency/ pancreatitis/ peritonitis/ pyelonephritis/ multiorgan failure	12
	Myocardial infarction	39
	Pulmonary thrombosis/ possible pulmonary embolism/ pulmonary embolism	3
	Ruptured aortic aneurysm	2
	Sepsis/ septic shock	6
	Shock/ dehydration	1
	Sudden death	6
	Traffic accident/ trauma/ polytrauma/ fracture of femur	8
	Unknown	24

*More than one in some cases

These 192 deaths were reported among more than 100,000 doxazosin or doxazosin GITS treated patients enrolled in Pfizer sponsored studies.

In eight of these cases in which the patient died, either the investigator or Pfizer attributed causality or relatedness of the reported events to doxazosin or doxazosin GITS. Five of these cases reported heart failure, myocardial infarction, stroke, or related events and are discussed above (#LOC 8900494, 9000181, 9000461, 9000723, 9000935). In case #9000879, a 78-year-old male patient with a history of angina or myocardial infarction and stroke died suddenly of unknown cause. A 56-year-old female patient (#9000994)

died of a ruptured aortic aneurysm. The eighth case (#8900549) reported non-cardiac events including "acute brain syndrome" and epilepsy and the 78-year-old male patient died of an unspecified condition of the brain.

Non-Clinical Study Cases

Initial review identified a total of 11,359 doxazosin or doxazosin GITS cases entered through 28 February 2001, of which 10,656 cases involved doxazosin and 703 cases involved doxazosin GITS. Of these, a total of 3,370 cases met the reporting criteria for a serious case. There were 11,243 cases spontaneously reported to Pfizer, 90 registry cases, and 26 cases published in the medical literature. To put his in perspective, during the 13 years that doxazosin has been commercially available when these cases were reported, there has been approximately 4.1 billion patient-days of doxazosin therapy. This gives an estimated reporting rate of 2,770 cases/billion patient-days of therapy.

Of the total of 11,359 cases, there were 3,464 that were reported to have involved at least one adverse cardiovascular event, of which 1,181 met the reporting criteria for a serious case. Hypertension was the reported indication (with or without a concurrent indication of BPH) for doxazosin/doxazosin GITS use in 3,329 cases. In 5,633 cases BPH (without concurrent hypertension) was the reported indication. The characteristics of these cases are summarized in Table 3.4 (below).

Table 3.4 Summary of Doxazosin and Doxazosin GITS Non-Clinical Study Cases Entered Into Pfizer's Early Alert Safety Database Through 28 February 2001.

Case Criteria	Number of Cases (% of All Cases)		
	Doxazosin	Doxazosin GITS	Total
Serious Cases[1]	3,215 (30.2%)	155 (22.0%)	3,370 (29.7%)
Hypertension Cases[2]	3,145 (29.5%)	184 (26.2%)	3,329 (29.3%)
BPH Cases[3]	5,314 (49.9%)	319 (45.4%)	5,633 (49.6%)
Cases with Heart Failure-Like Events	137 (1.3%)	11 (1.6%)	148 (1.3%)
Cases with Stroke-Like Events	184 (1.7%)	6 (0.9%)	190 (1.7%)
Cases with Myocardial Infarction or Related Events	146 (1.4%)	8 (1.1%)	154 (1.4%)
Cases with Cardiovascular Adverse Events	3,173 (29.8%)	291 (41.4%)	3,464 (30.5%)
All Cases	**10,656**	**703**	**11,359**

1 – Cases meeting the reporting criteria for a serious case.
2 – All cases where the reported indication coded to the ICD-9 diagnosis code "hypertensive disease". (Includes some cases where BPH was also reported as an indication.)
3 – Cases where the only reported indication coded to the ICD-9 diagnosis code "hyperplasia of the prostate".

As can be seen in Table 3.4, for doxazosin and doxazosin GITS the proportion of serious cases, cases where hypertension or BPH were the reported indications, and the proportion of cases reporting heart failure-like events, stroke-like events, or myocardial infarction or related events are similar.

The patient's ages were reported to be ≥ 55 years in 6,802 (60%) of all doxazosin/ doxazosin GITS cases, and in 2,472 (73%) of all cases that met the reporting criteria for a

serious case. The distribution of all individual cardiovascular adverse events reported in cases where the patient's ages were ≥ 55 years was similar to all cases as well as serious cases. For this reason, a separate review of these cases was not performed.

Concomitant therapy with a diuretic and/or at least one additional antihypertensive agent was reported in 3,261 (29%) of all doxazosin/doxazosin GITS cases, 889 (26%) of serious cases, 1,771 (53%) of all cases reporting hypertension as an indication, and 1,153 (20%) of cases reporting BPH as the indication.

Results—Non-Clinical Study Cases of Heart Failure-Like Events

Heart failure-like events were identified in a total of 148 cases (137 doxazosin cases and 11 doxazosin GITS cases), including events coding to the WHO-ART preferred adverse event terms "cardiac failure", "cardiac failure left", "cardiac failure right", "cardiomegaly", "circulatory failure", "cardiomyopathy", "hypertension pulmonary", "pulmonary edema", and "worsening heart failure". These events were reported in 1.3% of all doxazosin/doxazosin GITS cases entered into the database, with a reporting rate of 36 cases/billion patient-days of therapy. One hundred and twenty-three of these cases met the reporting criteria for a serious case. Of these 148 cases, 90 are excluded from further discussion for the following reasons:

Reason Case(s) Excluded	**Number of Cases**
Events involved acute circulatory collapse, shock-like conditions, orthostasis, or first dose syncope, NOT congestive heart failure.	28
Heart failure-like events reported in patients with pre-existing congestive heart failure, cardiac insufficiency, cardiomegaly, and/or left ventricular hypertrophy.	16
Heart failure-like events reported after discontinuation of doxazosin therapy.	15
The reported heart failure-like events were secondary to myocardial infarction, coronary heart disease, mitral valve disease, pericardial effusion, or septicemia	10
Events involved other circulatory problems, NOT congestive heart failure.	10
Cases that were poorly documented, missing information on age, daily dose, indication, concomitant medication, medical history, and event outcome.	4
Heart failure-like events were consequences of overdose/suicide attempt.*	2
Heart failure associated with β-blocker or verapamil therapy.	2
Non-specific events such as "tendency of cardiac failure" without details or decreased blood pressure considered as "an early sign of cardiac failure".	2
Patient experienced left ventricular hypertrophy prior to the initiation of doxazosin therapy.	1
Total Cases Excluded	**90**

* *One patient experienced pulmonary edema following an overdose of amlodipine 100 mg, the other patient experienced left ventricular arrhythmia, decreased blood pressure, and cardiocirculatory failure and subsequently died following ingestion of an unknown quantity of doxazosin as part of a suicide attempt.*

The remaining 58 non-clinical-study cases (54 doxazosin cases and 4 doxazosin GITS cases) of heart failure-like events were considered relevant for further discussion. The characteristics of these 58 relevant cases are summarized in Table 3.5 (below).

Table 3.5. Relevant Doxazosin Non-Clinical-Study Cases of Heart Failure-Like Adverse Events		
Characteristic		**Number of Cases**
Gender	Male	48
	Female	10
Age (years) range: 44-92	≤ 50	2
	51-70	17
	≥ 71	31
	Unknown	8
Indication *	Hypertension	20
	Benign Prostatic Hyperplasia	31
	Nocturia / Urinary Frequency	3
	"Blood pressure"	1
	Unknown	5
Dose of doxazosin Standard / doxazosin GITS at onset of Adverse Event	1 mg	7
	2 mg	27
	4 mg (standard/GITS)	10 / 4
	6 mg	1
	12 mg	2
	16 mg	1
	Unknown	6
Duration of therapy Prior to onset	≤ 7 days	4
	8-60 days	9
	61-365 days	18
	≥ 366 days	18
	Unknown	9
Outcome of adverse event	Resolved / improved	20
	Persisted	5
	Death	16
	Unknown	17
Relevant adverse event term*	Congestive heart failure / heart failure / cardiac failure	24
	Increased fluid in lungs / pulmonary edema / water in lungs	11
	Cardiac enlargement / cardiomegaly / hypertropic cardiomyopathy	10
	Cardiac insufficiency / decompensation	9
	Left ventricular failure / hypertrophy / insufficiency	7
	Cardiomyopathy	2
	Cardiac edema	1
	Pulmonary hypertension	1
Relevant concomitant medication*	Cases reporting use of relevant concomitant medications: Aspirin (8), furosemide (7), amlodipine (5), metoprolol (5), nifedipine (5), digoxin (4), captopril (3), chlorthalidone (3), glibenclamide (3), insulin (3), diltiazem (2), isosorbide dinitrate (2), losartan (2), methyldopa (2), troglitazone (2), atenolol, atorvastatin, benazepril, chlorpropamide, clonidine, enalapril, fluvastatin, hydrochlorothiazide, hydrochlorothiazide/enalapril, hydrochlorothiazide/triamterene, gemfibrozil, gliclazide, glipizide, imidapril, irbesartan, lisinopril, metformin, nilvadipine, prazosin, propatyl nitrate, quinapril, ramipril, sotalol, spironolactone, spironolactone/furosemide, unspecified angiotensin converting enzyme inhibitor, valsartan, verapamil	34

Table 3.5. Relevant Doxazosin Non-Clinical-Study Cases of Heart Failure-Like Adverse Events		
Characteristic		**Number of Cases**
Relevant medical history*	Cases reporting relevant medical history: Diabetes mellitus (14), hypertension (6), cardiac disease (4), hyperlipidemia/cholesterol disorder (4), obesity (2), tobacco use (2), anginal pectoris, atrioventricular block, arrhythmias, bronchial asthma, cardiac bypass surgery, cerebrovascular accident, chronic bronchitis, chronic cerebral ischemia, coronary artery disease, emphysema, myocardial infarction, myocardiopathy, pacemaker implantation, pulmonary fibrosis, transient ischemic attack	30

* More than one in some cases

Of these 58 relevant cases, 51 (88%) met the reporting criteria for a serious case. The patients in most of these cases were male (48 cases, 83%) and elderly (≥ 71 years; 31 cases, 53%). In 30 cases (52%), the patients were reported to have relevant medical histories for other conditions that might be associated with increased risk for heart failure. In 34 cases (59%), the patients were reported to have received relevant concomitant therapy with other medications reported to be associated with heart failure, or used to treat heart failure or other conditions that might be considered possible risk factors for heart failure. Some of the cases reported both relevant histories and concomitant medications.

Of the 52 cases where the information was provided, most of the patients (48 cases, 92%) were treated with ≤ 4 mg/day of doxazosin or doxazosin GITS. Of the 49 cases where the information on duration of therapy prior to onset of the heart failure-like events was provided, 36 cases (73%) involved patients who had been treated with doxazosin/doxazosin GITS for more than 60 days to up to five years. In three of these cases (#9402379, 9709442, 9812577), the onset of heart failure-like events was reported to have occurred after antihypertensive therapy with a diuretic and/or an ACE inhibitor was discontinued and doxazosin was started.

In 31 cases, the indication for doxazosin/doxazosin GITS was benign prostatic hyperplasia (BPH). While all of the BPH cases were males, the proportion of elderly cases (≥ 71 years; 20 cases, 65%) was similar to that of all cases. All of the BPH cases were treated with ≤ 4 mg/day of doxazosin or doxazosin GITS. Of the BPH cases, 52% (16 cases) reported pre-existing relevant medical conditions that might be associated with increased risk for heart failure, and 52% (16 cases) reported relevant concomitant therapy with other medications reported to be associated with heart failure, or used to treat heart failure or other conditions that might be considered possible risk factors for heart failure.

The patients were reported to have died in a total of 16 cases. Two of these cases reported death due to unknown cause on an unknown date; both cases involved female patients treated with doxazosin. In one case (#A101508), the patient died approximately three years after she was diagnosed with congestive heart failure, and it was unknown if the patient was still treated with doxazosin at the time of her death; in the other case (#A004756), the reporting physician stated that the patient did not experience any

adverse events with doxazosin. In another three cases, the patients died due to lung cancer (9922840), pulmonary emphysema (A011090), or multiple organ failure (#A020036), not the reported heart failure-like events. In the remaining 11 cases, the patients were reported to have died due to heart failure-like events. The patients were treated with doxazosin or doxazosin GITS for two months to up to two years prior to the event onset. All 11 cases involved male patients, and 73% (8 cases) were elderly. Five of these cases (45%) reported pre-existing relevant medical conditions that might be associated with increased risk for heart failure, and/or relevant concomitant therapy with other medications reported to be associated with heart failure, or used to treat heart failure or other conditions that might be considered possible risk factors for heart failure. In another three of these 11 cases (27%), no information was provided regarding the patients' concomitant medication use and medical history. Seven of these 11 cases were reported from a marketing-based patient compliance program that involved solicitation of information from consumers.

Results- Non-Clinical Study Cases of Myocardial Infarction-Like Events

Myocardial-infarction-like events were identified in a total of 154 cases (146 doxazosin cases and 8 doxazosin GITS cases) that involved events coding to the WHO-ART preferred adverse event terms "myocardial infarction", "myocardial rupture (post infarct)", and "thrombosis coronary". These events were reported in 1.4% of all doxazosin/doxazosin GITS cases entered into the database, with a reporting rate of 38 cases/billion patient-days of therapy. One hundred forty-one of these cases met the reporting criteria for a serious case. Of the 154 cases, 26 cases (23 doxazosin cases and 3 doxazosin GITS cases) are excluded from further discussion for the following reasons:

Reasons for Case Exclusion	**Number of Cases**
Cases poorly documented, missing information on age, gender, daily dose, indication, concomitant medication, medical history, and event outcome	7
Myocardial infarction pre-existing condition	9
Patient not taking doxazosin at time of myocardial infarction onset	1
Pre-existing history of angina or angina pectoris	3
Pre-existing history of cerebrovascular disease (transient ischemic attack, cerebral infarct, cerebral ischemia, stroke)	5
History of pulmonary embolism post surgery	1
Total Cases Excluded	**26**

The remaining 128 doxazosin/doxazosin GITS non-clinical-study cases of myocardial infarction-like events were considered relevant for further discussion. The characteristics of these 128 relevant cases are summarized in Table 3.6 (below).

Table 3.6. Relevant Doxazosin/Doxazosin GITS Non-Clinical-Study Cases Of Myocardial Infarction-Like Adverse Events		
Characteristic		**Number of Cases**
Gender	Male	124
	Female	4
Age (years) range: 42-86	≤ 50	5
	51-70	71
	≥ 71	41
	Unknown	11
Indication*	Benign Prostatic Hyperplasia (BPH)	112
	Hypertension	16
	Other	1
	Unknown	5
Dose of doxazosin standard/doxazosin GITS at onset of event	1 mg	3
	2 mg	91
	4 mg (standard/GITS)	18/5
	Unknown	4
Duration of therapy prior to onset of event	≤ 7 days	10
	8-60 days	10
	61-365 days	53
	≥ 366 days	37
	Unknown	17
Outcome of adverse event	Resolved / Improved	47
	Persisted	10
	Worsened	3
	Death	53
	Unknown	10
Relevant adverse event term*	Acute (multiple) myocardial infarction, acute myocardial infarction, acute cardiac infarction, cardiac arrest/infarct/infarction/infarction symptoms, fatal cardiac infarction/heart attack/myocardial infarction, heart attack, mild heart attack, sudden/possible/threatening myocardial infarction	122
	Angioplasty, arteriosclerosis, aortic aneurysm, calcification of artery, cardiac artery(ies)/ worsening cardiac artery/ cardiac vein/coronary artery/ obstruction or occlusion, coronary artery blockage, coronary artery disease, coronary artery occlusion, saphenous bypass cardiac surgery, thrombosis, vein obstruction	27
	Cardiomegaly, cardiovascular insufficiency, congestive heart failure/exacerbation cardiac failure, emphysema, heart valve disorder, mitral insufficiency, myxomatous aortic valve, peripheral edema, pneumonia, pulmonary edema, respiratory arrest, respiratory insufficiency, water in lungs, worsening aortic insufficiency	19
	Cardiac disease/disorders, worsening cardiac problem, heart disease, heart problem unspecified	8
	AV block, tachycardia, ventricular arrhythmia	6
	Angina pectoris, chest pain, unstable angina	9
	Anoxic encephalopathy, cerebral stroke, cerebrovascular accident, coma, syncope, convulsive crisis, faint, fall/accident, lightheadedness	11

Table 3.6. Relevant Doxazosin/Doxazosin GITS Non-Clinical-Study Cases Of Myocardial Infarction-Like Adverse Events		
Characteristic		**Number of Cases**
Relevant concomitant medications*	Cases reporting relevant concomitant medications: Isosorbide mononitrate (7), diltiazem (6), amlodipine (5), captopril (4), enalapril (4), hydrochlorothiazide (4), nifedipine (4), propatyl nitrate (4), amiodarone (3), aspirin (3), atenolol (3), isosorbide dinitrate (3), metoprolol (3), spironolactone (3), propanolol (2), verapamil (2), acebutolol, amiloride, amiloride/hydrochlorothiazide, atorvastatin, bendrofluazide, bendrofluazide/potassium, candesartan, cardiovascular drug unspecified, chlorthalidone, digoxin, fosinopril, furosemide, hydralazine, lisinopril, minoxidil, pentaerythritol tetranitrate, ramipril, simvastatin, terazosin, timolol, warfarin	49
Relevant medical history*	Cases reporting relevant medical history : History of cardiovascular disease/disorders (25, including coronary vessel obstruction or blockage, arteriosclerosis, bypass surgery, valvular defects, rheumatic heart disease, enlarged heart, ischemic heart disease, congestive cardiac or heart failure, and coronary artery disease), diabetes (20), history of hypertension in patients treated for BPH (17), Pre-existing arrhythmias (5, including atrial fibrillation, premature ventricular contractions, irregular rhythms), history of smoking/tobacco use (3), hypercholesterolemia (3), obesity/ overweight (3), resistant hypertension	48

* More than one in some cases

Of the 128 relevant cases, all 128 (100%) met the reporting criteria for a serious case. Ninety-three (73%) of the relevant cases were reported via marketing-based patient compliance programs. These programs involve solicitation of information from consumers regarding their prescription drug use, including any adverse events they may have experienced regardless of causality. Of the 93 compliance program cases reported, 63 cases (68%) were lacking key information regarding concomitant medication and/or medical history. In many of these cases it was unclear whether a physician or healthcare professional had diagnosed the reported events.

The patients in the majority of the 128 relevant cases were male (124 cases, 97%) and/or were $\geq$ 51 years of age (112 cases, 88%). The treatment indication cited for the majority of patients was BPH (112 cases, 88%). In 48 (38%) of all relevant cases, the patients were reported to have relevant medical histories for other conditions that might be associated with increased risk for myocardial infarction or myocardial infarction-like events. Of those cases reporting significant medical histories, 17 cases reported hypertension and one case reported resistant hypertension, 20 cases cited pre-existing diabetes, 5 cases of documented arrhythmias (such as atrial fibrillation and premature ventricular contractions), and 34 cases cited smoking, obesity, hypercholesterolemia, unspecified cardiac or circulatory disorders, or coronary heart disease. In 38% of the relevant cases (49 cases), the patients were reported to have received relevant concomitant therapy with other medications reported to be used to treat other conditions

that might be considered possible risk factors for myocardial infarction. In some cases, both relevant histories and concomitant medications were reported.

Of the 128 relevant cases, patients in 94 cases (73%) were treated with ≤ 2mg/day of doxazosin or doxazosin GITS. Information regarding the duration of therapy prior to onset of the myocardial infarction and myocardial infarction-like events was provided in 110 cases (86% of the relevant cases) of which 90 patients were treated for greater than 60 days.

Of all relevant cases, 112 cases (88%) cited the indication for doxazosin/doxazosin GITS as BPH. The majority of these cases (89 cases, 79%) originated from the aforementioned marketing-based patient compliance programs and lacked key information and verification by health professionals. All BPH patients appeared to have one or more risk factors for myocardial infarction based on gender (all 112 patients were males) and age ≥ 51 years (96 cases, 86%), significant medical histories (48 cases, 43%) including diabetes, smoking, obesity, pre-existing cardiovascular disease, arteriosclerosis, coronary bypass surgeries, hypertension, and hypercholesterolemia, and relevant concomitant medications suggestive of concurrent illness that is a risk factor for myocardial infarction such as hypertension or coronary heart disease (42 cases, 38%).

Patients were reported to have died in a total of 54 cases (42% of all relevant cases), of which 51 (94%) patients appear to have died as a result of the reported myocardial infarction-like events. Of all cases reporting death, 39 cases (72%) originated from the aforementioned marketing-based patient compliance programs and lacked key information and verification by health professions. In three cases, the cause of death was attributed to something other than myocardial infarction-like events. In one case (#A002736), pneumonia was cited among a number of complications as the cause of death after a 78-year-old male patient had suffered two myocardial infarctions approximately four and eight months prior. In a second case (#9916801), the patient experienced coma and died while waiting for scheduled bypass surgery approximately three weeks after reporting myocardial infarction symptoms. The third case (#9834370) reported death due to unknown causes approximately three months after experiencing myocardial infarction. In six cases, cause of death was attributed to myocardial infarction-like events in addition to stroke (#A103998), cerebrovascular accident (#9938943), pneumonia (#A010163, 9934642), respiratory insufficiency (#9905412), or septicemia (#39927237).

As for all relevant cases of myocardial infarction-like events, the patients in those relevant cases in which patients died were mostly male (91%) and/or age ≥ 51 years (91%), cited BPH as the indication for doxazosin/doxazosin GITS (87%). In 37 cases (69%), patients took ≤ 2mg/day of doxazosin. In addition, 12 cases (22%) cited significant medical histories for risk factors for myocardial infarction as well as 14 cases (26%) in which relevant concomitant therapy with other medications reported to be used to treat other conditions that might be considered possible risk factors for myocardial infarction. In five cases (9%), both relevant histories and concomitant medications were reported.

Results—Non-Clinical Study Cases of Stroke-Like Events

Stroke-like events were identified in a total of 190 cases (184 doxazosin and 6 doxazosin GITS cases) that involved events coding to the WHO-ART preferred adverse event terms "cerebral hemorrhage", "cerebrovascular disorder", "embolism cerebral", "hemorrhage intracranial", "subarachnoid hemorrhage", "thrombophlebitis cerebral vein", "thrombosis carotid", "thrombosis cerebral", and "thrombosis cerebral arterial". These events were reported in 1.7% of all doxazosin/doxazosin GITS cases entered into the database, with a reporting rate of 46 cases/billion patient-days of therapy. A total of 179 of these cases met the reporting criteria for a serious case. Of the 190 cases, 20 were excluded from further discussion for the following reasons:

Reason Case(s) Excluded	**Number of Cases**
The event preceded doxazosin therapy or it cannot be determined from the report when the event occurred relative to doxazosin therapy.	2
Upon follow-up, the event did not occur.	3
The event was reported to be secondary to head trauma.	4
The events occurred four to six months after only one dose of doxazosin was taken then discontinued.	1
The events occurred and the patient died following an intentional overdose of an unknown amount of doxazosin.	1
The reported head circulatory difficulty was reported to be due to a neck node developed many years prior to therapy.	1
The events were reported to be due to a congenital arteriovenous malformation.	1
The reporting physician did not believe the events to have any relationship to doxazosin and added that the patient had a history of blaming and reporting drugs for medical problems.	1
The patient was reported to have a history of recurrent brain stem strokes which continued (but did not worsen) upon initiation of doxazosin.	1
The case was poorly documented, missing information on age, daily dose, indication, concomitant medication, medical history, and event outcome; gender was also missing in one of the cases.	5
Total Cases Excluded	**20**

The remaining 170 non-clinical study cases (164 doxazosin and six doxazosin GITS) of stroke-like events were considered relevant for further discussion. The characteristics of these 170 relevant cases are summarized in Table 3.7 (below).

Table 3.7. Relevant Doxazosin/Doxazosin GITS Non-Clinical-Study Cases Of Stroke-Like Adverse Events

Characteristic		**Number of Cases**
Gender	Male	146
	Female	23
	Unknown	1
Age (years) range: 12-93	≤ 50	3
	≥ 51 to ≤ 70	67
	≥ 71	78
	Unknown	22

Table 3.7. Relevant Doxazosin/Doxazosin GITS Non-Clinical-Study Cases Of Stroke-Like Adverse Events		
Characteristic		**Number of Cases**
Indication*	Hypertension	46
	BPH	113
	Neurogenic bladder	1
	Unknown	12
Dose of doxazosin standard /doxazosin GITS at onset of event	1 mg	14
	2 mg (standard/GITS)	104 / 2
	4 mg (standard/GITS)	28 / 3
	8 mg	6
	16 mg	1
	Unknown (standard/GITS)	17 / 1
Duration of therapy prior to event	≤ 7 days	11
	8-60 days	21
	61-365 days	50
	≥ 366 days	48
	Post discontinuation	9
	Unknown	31
Outcome of Adverse event	Resolved / Improved	61
	Persisted / Disability	28
	Worsened	3
	Death	37
	Unknown	41
Relevant adverse event*	Cerebrovascular accident	67
	Cerebral stroke/ stroke/ ischemic stroke/ mini-strokes/ stroke behind left eye	31
	Cerebral ischemia	19
	Brain stem infarction/ cerebral infarction(s)	7
	Apoplectic insult/ apoplexy	2
	Bleeding in the brain/ hemorrhagic stroke/ intracerebral hemorrhage/ subdural hematoma	3
	Suspected infarct basal ganglia/ suspected split cerebral aneurysm/ suspected transient ischemic attack	10
	Transient ischemic attack(s)	9
	Carotid obstruction/ carotid artery obstruction/ left internal carotid artery occlusion/ cerebral clot/ cerebral thrombosis	6
	Cerebrovascular accident symptoms	6
	Possible cerebrovascular accident/ possible posterior cerebral ischemia/ possible stroke/ possible transient ischemic attack(s)	6
	Cerebral ischemia symptoms/ stroke-like symptoms	3
	Cerebral anemia	1
	Cerebral hypoxia	1
	Cerebral paralysis	1
	Cerebrovascular attack	1
	Cerebrovascular event	1
	Progression of left carotid artery blockade	1
	Recurrent cerebral infarction	1
	Sequela of cerebral infarction	1
	Transient ischemic attack-like symptoms	1
	White matter (brain) ischemic change	1

Table 3.7. Relevant Doxazosin/Doxazosin GITS Non-Clinical-Study Cases Of Stroke-Like Adverse Events		
Characteristic		**Number of Cases**
Relevant concomitant medication*	Cases reporting use of relevant concomitant medications: Aspirin (14), digoxin (11), enalapril (11), amlodipine (9), captopril (7), nifedipine (7), warfarin (6), chlorthalidone (4), furosemide (4), isosorbide dinitrate (4), insulin (4), atorvastatin (3), clopidogrel (3), diltiazem (3), glibenclamide (3), lisinopril (3), pravastatin (3), verapamil (3), benazepril (2), bendrofluazide (2), labetalol (2), medigoxin (2), metoprolol (2), nitroglycerin (2), phenytoin (2), potassium (2), propranolol (2), simvastatin (2), unspecified antihypertensive drug(s) (2), alcohol, alacepril, amiodarone, anavenol, arotinolol, atenolol, bezafibrate, chlorpropamide, coumarin, delapril, dipyridamole, efonidipine, flunarizine, fluvastatin, gemfibrozil, gliclazide, glipizide, hydrochlorothiazide/losartan, hydrochlorothiazide/triamterene, isosorbide mononitrate, magnesium oxide/ acetylsalicylic acid, metformin, methyldopa, mibefradil, nateglinide, sildenafil, spironolactone, tolbutamide, torasemide, valsartan, unspecified hypoglycemic drug	73
Relevant medical history*	Cases reporting relevant medical history: Hypertension (28), diabetes (21), tobacco smoking (5), atrial fibrillation (4), cerebrovascular accident (4), coronary artery disease (4), circulatory disorders (4), bypass surgery (4), hypercholesterolemia (4), congestive heart failure (3), hyperlipidemia (3), ischemic heart disease (2), stroke (2), transient ischemic attack (2), adverse drug reaction to antihypertensive medication, cardiac disorders, cardiac insufficiency, cardiomyopathy, cerebral infarction with hemiplegia, cholesterol increase, dysrhythmia, heart disease, impaired fasting glucose, lipometabolic disorders, metal fume fever, myocardial infarction, peripheral vascular disease, two previous strokes, valve in the head implant, venous insufficiency, unspecified cardiac disorders	75

*More than one in some cases

Of the 170 relevant cases, 162 (95%) met the reporting criteria for a serious case. A total of 92 (54%) of the 170 relevant cases were reported via marketing-based patient compliance programs that involve solicitation of information from consumers regarding their prescription drug use, including any adverse events they may have experienced regardless of causality. Many of these cases lacked key information regarding concomitant medication and medical history. In some of these cases it was unclear whether a physician had diagnosed the reported events.

Most patients were male (86%) and/or $\geq$ 51 years of age (85%). The treatment indication for 46 cases (27%) was hypertension, a major risk factor for stroke. Though the treatment indication for the majority of cases was BPH (113 cases, 66%), 23 of these cases reported a medical history of hypertension and 25 reported a medical history of diabetes, smoking, unspecified cardiac or circulatory disorders, or coronary heart disease. In nine additional cases, the patients were taking concomitant medication(s) suggestive of concurrent illnesses that are risk factors for stroke such as hypertension or coronary heart disease. In one case where BPH was the treatment indication, the patient had experienced a stroke prior to treatment with doxazosin. Many of the cases reporting BPH

as the treatment indication originated from the aforementioned compliance programs and lacked key information and verification by health professionals. Overall, 161 cases (95%) reported at least one risk factor for stroke, with 87 cases (51%) reporting three or more possible risk factors.

The dose in most of the 170 cases (69%) was 2 mg or less doxazosin daily. In 57 cases (34%), the patients were reported to be taking at least one additional antihypertensive agent.

There was a total of nine cases in which the patient had a medical history of stroke, cerebrovascular accident, cerebral infarction, or transient ischemic attack prior to the initiation of doxazosin therapy (#9100955, 9912463, 9919606, 9930999, 9938428, 9939012, A012288, A026392, A026679).

Alternate etiologies for the events were reported in three cases. In case #A008947, the physician reported that the events were secondary to atrial fibrillation. The suspected transient ischemic attack in case #A104243 may actually have been autonomic imbalance due to diabetes, according to the reporting physician. The reporting physician in case #9808144 suspected that the brain stem infarction was caused by cerebrovascular stenosis. There were six additional cases that were notable for various reasons. In case #9916033, the event, "white matter (brain) ischemic change", was reported not to be of clinical significance. A consumer reported that breathlessness was diagnosed as symptoms of stroke in case #9836763. The patient in case #A018780 was reported to have had a valve implanted in his head approximately nine years prior to the events about which no further information was provided. A cranial CT scan revealed no abnormality in case #9932287 and no evidence of an infarction or hemorrhage in case #9949683. The patient was reported to have died in the latter case. In case #A007411, a carotid exam revealed an obstruction to the patients' brain.

In nine cases, the events occurred after the discontinuation of doxazosin therapy (#9701743, 9802466, 9839516, 9920911, 9926355, 9935542, 9945184, 9950033, A016870). One of these patients was reported to have died (#9802466). One patient took doxazosin for only two days, and the apoplectic insult occurred two days after cessation of therapy (#9701743). The events occurred from six days to within two months of stopping therapy in seven cases and in the last case the duration between cessation and the event was unknown. The reporting physician in case #9920911 did not suspect doxazosin as the cause of the reported bleeding in the brain.

There were 17 cases in which the duration of therapy prior to onset of events was less than or equal to one month, two of which reported death as the outcome (#9902469, A014436). In 16 cases, the patients had risk factors that indicated they might have been at risk for the reported events independent of doxazosin therapy. In 14 of these cases, the patients had a medical history of hypertension, diabetes, atrial fibrillation, or prior cerebral infarction or TIA (two cases). In case #A032829, an ultrasonography of the patient's neck vessels revealed atheromatous plaques. Case #A101246 reported that the events occurred concurrently with consumption of a higher than normal amount of

alcohol. In the seventeenth case (#9623708) in which a 75-year-old male experienced a cerebral infarction one half hour after taking an "unknown amount of" doxazosin tablets, the medical history, concomitant medications, duration of therapy, and outcome were unknown.

There were a total of 37 cases in which the patient was reported to have died. In nine of these cases the cause of death was reported not to be related to stroke-like events or cerebrovascular disease. Doxazosin had been discontinued prior to the patients' death in seven of these nine cases. In 28 cases, the patients were reported to have died of cerebrovascular disease or related events. There was one case in which the reported events (#9842067, suspected split cerebral aneurysm) may have occurred subsequent to head trauma. In case #9621592, the 56-year-old female died of a ruptured cerebral aneurysm and intracranial hemorrhage. The physician reported that she was to have discontinued benazepril and amlodipine therapy upon initiation of doxazosin therapy but that one or both may have been continued due to "patient confusion". The onset of events was approximately three weeks after cessation of doxazosin therapy in case #9802466 and the patient subsequently died of a cerebral artery occlusion. In case #9912203, the patient experienced one cardiovascular accident (CVA) while on doxazosin but also four additional CVAs after doxazosin was discontinued and subsequently died. In case #9915742, the 65-year-old male treated with 2 mg daily doxazosin for BPH experienced a cerebrovascular accident while being hospitalized for hypertension and subsequently died. In three cases (#9919606, A014056, A026392), the patients had a history of CVAs prior to initiation of doxazosin therapy. A male of unknown age experienced a cerebrovascular accident during an airplane flight in case #9808282 in which the concomitant medications and medical history were unknown. Eighteen of the remaining 19 cases were reported by consumers in Brazil or Chile, mainly via the aforementioned patient compliance programs, and lacked important information as well as physician verification. Overall, the outcome of death in these cases did not appear to be associated with doxazosin therapy.

Discussion

A search of the Pfizer early alert safety database identified 99 serious Pfizer-sponsored clinical study cases with cardiovascular events in which the investigator and/or Pfizer attributed causality or relatedness of the events to doxazosin or doxazosin GITS therapy (see Table 3.2). The most commonly reported events (in 10 or more cases) among these 99 serious doxazosin/doxazosin GITS Pfizer-sponsored clinical study cases reporting adverse cardiovascular events (86 doxazosin and 13 doxazosin GITS) were angina pectoris/angina pectoris aggravated, cerebrovascular disorder, syncope, hypotension/ hypotension postural, myocardial infarction/thrombosis coronary, chest pain, and atrial/ventricular fibrillation. These events have been reported to be associated with doxazosin therapy, and are listed in the current doxazosin and doxazosin GITS labeling.[1,2]

Of the 99 serious Pfizer-sponsored clinical study cases, seven involved heart failure-like events, 13 involved myocardial infarction, and 18 involved stroke-like events or related events. Due to multiple events in three cases, there were 34 cases that reported these

three types of events. In nearly all 34 cases, the patients had a concomitant medication(s) or medical history suggestive of pre-existing cardiovascular disorders or other risk factors associated with these events. The treatment indication in all but one of the 34 cases was hypertension. Therefore, these patients appeared to be at high risk of developing heart failure, myocardial infarction, stroke, or related events independent of doxazosin or doxazosin GITS therapy, and there is no signal of a causal relationship between these events and doxazosin or doxazosin GITS therapy. In addition, based on review of the cases in which the patient was reported to have died regardless of causality, there is no signal indicating that doxazosin or doxazosin GITS therapy places patients at increased risk of death.

A search of the Pfizer early alert safety database identified a total of 11,359 doxazosin and doxazosin GITS non-clinical-study cases (10,656 cases and 703 cases, respectively) entered into the database as of 28 February 2001. These cases were reported over the 13 years that doxazosin has been commercially available and following approximately 4.1 billion patient-days of doxazosin therapy. This gives an estimated reporting rate of 2,770 cases/billion patient-days of therapy. About 30% of these cases met the reporting criteria for a serious case. The treatment indication cited for the majority of doxazosin/doxazosin GITS cases, was BPH (50%, 5,633 cases), with 29% of cases reporting hypertension as the indication (3,329 cases). The patient's ages were reported to be $\geq$ 55 years in 60% of the cases, and the distribution of all individual cardiovascular adverse events in these cases was similar to that of all cases. Concomitant use of a diuretic and/or at least one other antihypertensive agent was reported in 29% of all cases, 26% of serious cases, 53% of cases where hypertension was reported as an indication, and in 20% of cases where BPH was the indication.

A total of 148 cases of heart failure-like events were reported, representing 1.3% of all doxazosin/doxazosin non-clinical study cases, with a reporting rate of about 36 cases/billion patient-days of therapy. Of the 58 relevant non-clinical-study cases reporting heart failure-like events, the majority was male and elderly. This is not entirely unexpected, since heart failure is more common in men and in the elderly.[3,4] Most of these cases, as with the Pfizer-sponsored clinical study cases, were treated with fairly low daily doses of doxazosin or doxazosin GITS suggesting that due to possible suboptimal dosing, hypertensive patients and BPH patients with a history of hypertension could have had their blood pressure inadequately controlled at the time of the events. Most of the cases had medical histories that appear to have placed the patients at high risk for heart failure-like events. The number of cases where the indication for use of doxazosin/doxazosin GITS was BPH was slightly higher than the number of cases where the indication was hypertension. Separate review of the cases of heart failure-like events where the indication was BPH found that these cases were mostly elderly and also had medical histories suggestive of high risk for these events. It is not entirely unexpected that at least some BPH patients treated with doxazosin/doxazosin GITS would be at high risk for heart failure-like events. Since the prevalence of BPH increases with age,[5] it is not unexpected that at least some BPH patients would have concurrent cardiovascular disease that would be associated with an increased risk of heart failure, as well as for myocardial infarction and stroke. Also, for the 11 cases where the patients died as a

result of the heart failure-like events, the patients were mostly males and elderly, and many were reported to have medical histories that would place them at high risk of heart failure-like events.

Acute myocardial infarction is one of the most common diagnoses in hospitalized patients in industrial nations.[6] Of the non-clinical study cases reported to Pfizer, there were 154 non-clinical study cases reporting myocardial infarction-like events which were reviewed. These 154 cases represent 1.3% of all doxazosin/doxazosin non-clinical study cases, with a reporting rate of about 38 cases/billion patient-days of therapy. Of these 154 cases, 112 (88%) were indicated for BPH. This dataset was notable for the nearly 75% of cases originating from marketing-based patient compliance programs. These were reported by consumers and most lacked information regarding concomitant medication and medical history. Most of these patients were male, age $\geq$ 51 years, and had risk factors for developing myocardial infarction-like events independent of doxazosin or doxazosin GITS therapy, based on significant medical histories and relevant concomitant therapies. This dataset was notable for the nearly 75% of cases originatin from market-based patient compliance programs. These were reported by consumers and most lacked information regarding concomitant medications and medical history. There were 54 patients who were reported to have died, and this outcome did not appear to be associated with doxazosin therapy in these cases. The mortality rate of acute myocardial infarction is approximately 30% with more than half of these deaths occurring before the patient even reaches the hospital.[6] Given that most patients were at risk for myocardial infarction-like events, and the majority of these cases originated from marketing-based patient compliance programs and were lacking key information regarding concomitant medication and/or medical history, there was no signal of a causal relationship with doxazosin or doxazosin GITS.

Stroke events occur predominately in the middle to later years of life with the incidence of stroke increasing with age. Hypertension is also a risk factor of great importance.[7] There was a total of 170 non-clinical study cases reporting stroke-like events, representing 1.7% of all doxazosin/doxazosin non-clinical study cases, with a reporting rate of about 46 cases/billion patient-days of therapy. Not surprisingly, most of these patients were male and age $\geq$ 51 years. Also, the majority of patients had a medical history or were taking medication(s) suggestive of concurrent illness that could have predisposed them to the reported events independent of doxazosin and doxazosin GITS therapy. In most cases, the daily dose was low, suggesting that due to possible suboptimal dosing, some of the patients could have had inadequately controlled blood pressure at the time of the events. This dataset was notable in that over half of the cases (89/170) originated from market-based patient compliance programs. For the 37 cases in which the patient was reported to have died, this outcome did not appear to be associated with doxazosin/doxazosin GITS therapy. These were reported by consumers and most lacked information regarding comedication and medical history. Overall, there was no signal of a causal relationship between stroke-like events and doxazosin/doxazosin GITS therapy.

Conclusion

The number of cases reported to Pfizer that involved heart failure-like events, myocardial infarction-like events, and stroke-like events was small compared to all reported cases of adverse events, and the characteristics of the patients suggest that they were at high risk of experiencing these selected cardiovascular events independent of doxazosin/doxazosin GITS therapy. The number of these cases is very small considering the more than 4.1 billion patient-days of doxazosin therapy over 13 years of worldwide commercial use. Review of the cases of heart failure-like events, myocardial infarction-like events, and stroke-like events supports the conclusion of the review of Pfizer's clinical trials databases that there is no signal of a causal relationship between these select cardiovascular events and doxazosin or doxazosin GITS therapy. In addition, based on review of all cases in which the patient was reported to have died, there is no signal indicating that doxazosin or doxazosin GITS therapy places patients at increased risk of death.

References

1) Doxazosin Mesylate International Product Information (#154). Pfizer Inc, 3 May 2000.

2) Doxazosin Mesylate GITS International Product Information (#154). Pfizer Inc, 3 May 2000.

3) Braunwald E. Heart failure. *Harrison's Principles of Internal Medicine (14th Ed).* Fauci AS, Braunwald E, Isselbacher KJ *et al* (Eds). Mc-Graw-Hill: New York. 1998. Pg. 1287-1298.

4) Johnson JA, Parker RB, and Geraci SA. Heart failure. *Pharmacotherapy: A Pathophysiologic Approach (4th Ed).* DiPiro JT, Talbert RL, Yee GC *et al* (Eds). Appleton & Lange: Stamford, Connecticut. 1999. Pg. 153-181.

5) Sagalowsky AI and Wilson JD. Hyperplasia and carcinoma of the prostate. *Harrison's Principles of Internal Medicine (14th Ed).* Fauci AS, Braunwald E, Isselbacher KJ *et al* (Eds). Mc-Graw-Hill: New York. 1998. Pg.596-602.

6) Antman EM and Braunwald E. Acute myocardial infarction. *Harrison's Principles of Internal Medicine (14th Ed).* Fauci AS, Braunwald E, Isselbacher KJ *et al* (Eds). McGraw-Hill: New York. 1998. Pg. 1352-1364.

7) Easton JD, Hauser SL, and Martin JB. Cerebrovascular disease. *Harrison's Principles of Internal Medicine (14th Ed).* Fauci AS, Braunwald E, Isselbacher KJ *et al* (Eds). McGraw-Hill: New York. 1998. Pg. 2325-2348.